CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22404Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA: 22-404	Submission Date: 06/15/09
Submission Type:	505(b)(2)
Brand Name:	Oravig®
Generic Name:	Miconazole
Primary Reviewer:	Yoriko Harigaya, Pharm.D.
Team Leader:	Philip Colangelo, Pharm.D., Ph.D.
OCP Division:	Division of Clinical Pharmacology 4
ORM Division:	Division of Special Pathogen and Transplant Products
Sponsor:	BioAlliance Pharma
Relevant IND(s):	N/A
Formulation; Strength:	Buccal Tablet 50mg
Proposed Indication:	Treatment of oropharyngeal candidiasis
Proposed Dosage Regimen:	• Apply a single tablet to the gum once daily in the morning for 14 consecutive days. • Apply 2nd tablet when dislodgement of the first tablet occurs within 6 hours.

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1. EXECUTIVE SUMMARY

1.1. Recommendations

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 4 (OCP/DCP 4) has reviewed NDA 22-404 submitted on 06/15/09 for miconazole 50 mg buccal tablet (Oravig®). From an OCP perspective, the clinical pharmacology information contained in the application is acceptable provided that a satisfactory agreement can be reached with the applicant regarding the labeling.

1.2. Phase IV Commitments

No phase IV commitments are recommended.

1.3. Summary of Clinical Pharmacology and Biopharmaceutics Findings

BioAlliance Pharma, Inc. has submitted NDA 22-404 for Oravig, buccal tablet 50mg, for the local treatment of oropharyngeal candidiasis (OPC), as a 505(b)(2) application. The proposed dosing regimen for Oravig is a once daily 50 mg tablet application to upper gum just above the right or left incisor tooth in the morning for 14 consecutive days.

Miconazole is marketed in various prescription and over-the-counter products in over 100 countries and has been approved in the United States since 1974 under various trade names including Monistat® (vaginal formulations) and Micatin® (dermal formulations). Miconazole has been marketed in the European Union since 1973 under the trade name of Daktarin® (oral gel, topical formulations, and vaginal formulations). Miconazole can also be administered orally, intravenously, or intrathecally; however, in the US, miconazole is either currently available for external dermal application and indicated for fungal skin infections (such as tinea versicolor, serpigo, tinea cruris, and tinea pedis) or may be applied intravaginally for the treatment of vaginal thrush. Millions of patients in numerous countries, including Europe and the United States, have been treated with products containing miconazole and a favorable safety profile is well established. To support the approval in accordance with 505(b)(2) regulations, the sponsor is relying on the previous findings of safety and efficacy of Monistat® (vaginal formulations) and Daktarin® (oral gel not approved in U.S.).

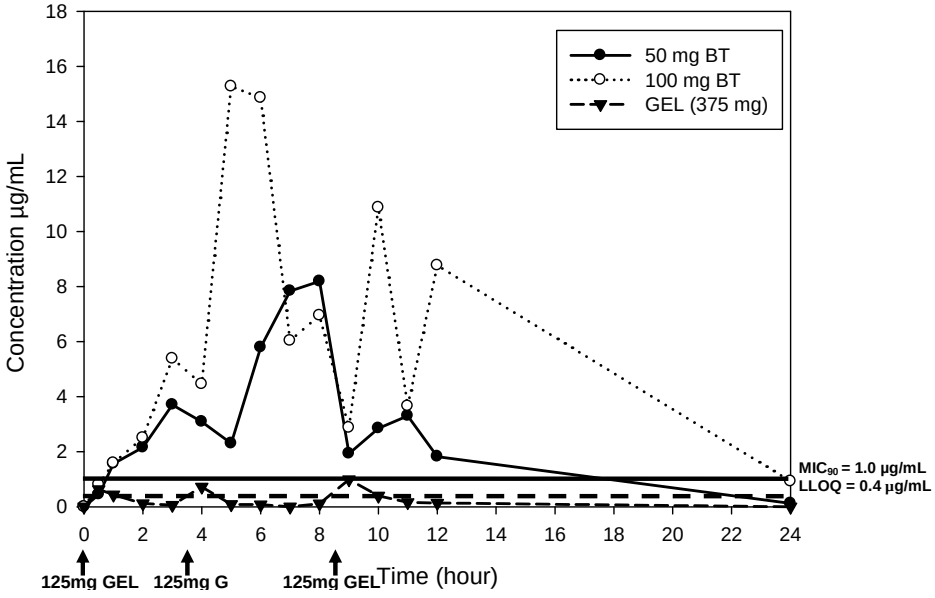
The one Clinical Pharmacology study (BA2000/01/01) in 18 healthy volunteers was conducted to obtain pharmacokinetic (PK) data to support the NDA. This study provides the pharmacokinetic (PK) profile of Oravig 50 mg and 100 mg in plasma and saliva in healthy subjects. Oravig 50 mg (once daily) salivary exposures (AUC_{0-12} & AUC_{0-24}) to miconazole were greater than 10 times that achieved with the oral gel (Daktarin® 125mg three times daily) formulation. The plasma concentrations obtained after administration of Oravig 50 mg and 100 mg in Study BA2000/01/01 were below the limit of quantification (LOQ = 0.4 μg/mL) for over 97% of the samples collected. In 2 Phase 3 studies (BA2004/01/04, BA2002/01/03) with Oravig 50 mg, plasma concentrations of miconazole from 40 HIV positive patients were essentially undetectable (LLOQ = 0.1 μg/mL).

The PK profile of miconazole in the saliva of healthy volunteers evaluated in Study BA2000/01/01 is displayed in the table and graph below.

Study BA2000/01/01
Pharmacokinetic parameters in saliva following application of Oravig 50 mg, 100 mg or Gel

	BA001- 50	BA001- 100	Gel
C_{max} (µg/mL)			
Mean	**15.07**	**39.06**	**1.61**
Standard deviation	16.21	49.29	1.62
[min-max]	[0.45-64.75]	[1.72-179.51]	[0-6.59]
CV (%)	107.56	126.20	100.92
50 or 100 vs gel	*p<0.0001*		
50 vs 100	*p=0.001*		
t_{max} (h)			
Median	**7**	**6**	**4#**
[min-max]	[2-24.13]	[3-12]	[0.5-9]
AUC (0-12) (µg.h/mL)			
Mean	**42.97**	**78.62**	**3.43**
Standard deviation	31.99	78.42	4.14
[min-max]	[0-117.33]	[2,01-244.05]	[0-13.87]
CV (%)	74.45	99.74	120.91
50 or 100 vs gel	*p<0.0001*		
50 vs 100	*NS (p=0.06)*		
AUC (0-24) (µg.h/mL)			
Mean	**55.23**	**136.16**	4.25
Standard deviation	35.09	149.54	6.49
[min-max]	[0.45-128.32]	[2.01-606.96]	[0-24.19]
CV (%)	63.54	109.82	152.07
50 and 100 vs gel	*p<0.0001*		
50 vs 100	*p=0.01*		

Mean Concentration of Miconazole in Saliva



Study BA2000/01/01 demonstrated prolonged release of miconazole from Oravig buccal tablet into saliva with low systemic absorption. Additionally, Oravig 50 mg adhesion time and acceptability for the subjects were preferred more than Oravig 100 mg. These results supported the 50 mg tablet as the more appropriate dose for the Phase III clinical development program (BA2004/01/04, BA2002/01/03, BA2002/01/02).

Overall, the information submitted in this application is acceptable, provided that a satisfactory agreement can be reached with the applicant regarding the labeling.

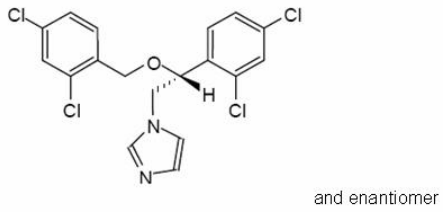
2. QUESTION BASED REVIEW

2.1. General Attributes of the Drug

What is Oravig, and what is the proposed indication and dosing regimen?

Oravig 50 mg has been developed for the local treatment of oropharyngeal candidiasis (OPC). Miconazole, the active ingredient in Oravig 50 mg, is a synthetic imidazole antifungal agent. The Oravig utilizes a unique delivery system to adhere to the buccal mucosa and to provide extended-release of miconazole in the oral cavity. The proposed rationale for Oravig 50 mg is that it provides miconazole saliva concentrations higher and longer than those obtained with miconazole 125 mg oral gel, and Oravig 50 mg could meet the unmet medical needs of patients suffering from OPC by offering them a once-daily treatment that would improve patient compliance and lead to enhanced antifungal efficacy.

Structural Formula of Miconazole



and enantiomer

OPC is the most frequent *Candida* infection. If left untreated, OPC may invade the esophagus or further progress to induce systemic complications. Oral manifestations can consist of any or a combination of the following: erythematous lesions or pseudomembranous lesions called thrush. The main predisposing factor involved in the conversion of oral commensal *Candida* to a parasitic form is an alteration of the immune status of the host. This may be associated with age, malnutrition, chemotherapy, immunosuppressive agents or severe disease such as HIV.

Oravig 50 mg must be applied to the gum once daily for 14 consecutive days. Oravig is a hard, white to off-white tablet, having width of approximately 8 mm. The tablet adheres to the upper gum just above the incisor tooth with the flat surface facing the cheek mucosa. For proper use, the Oravig must adhere to the buccal mucosa and remain place, intact, for an extended period of time ranging up to and beyond 12 hours. With each application, Oravig should be applied to alternate sides of the gum. The tablet will slowly dissolve over time and should be left in place—there is no need to remove the tablet. If Oravig does not stick or falls off within the first 6 hours the same tablet should be repositioned immediately. If Oravig is swallowed within the first 6 hours it is recommended to drink a glass of water and a new tablet should be applied only once. If Oravig falls off or is swallowed after it was in place for 6 hours or more a new tablet should not be applied until the next, regularly scheduled dose.

To attain the extended release properties of Oravig 50 mg tablets, hypromellose, maize starch, and MPC were selected as the main functional excipients of the formulation. (b) (4) hypromellose was chosen to (b) (4) (b) (4)

(b) (4)

(b) (4) The abrupt release of the 50 mg miconazole from the tablet is therefore very unlikely.

Different direct compression formulations were evaluated with the minimum quantities of excipients to evaluate the behavior of the (b) (4) An optimized ratio of (b) (4) was used to provide an *in vitro* linear release of miconazole up to 5 hours and an extended release up to 8 hours with a tablet (b) (4) (b) (4) The presence of (b) (4) SLS improves the (b) (4) (b) (4). Percentages of magnesium stearate ((b) (4) and talc ((b) (4) were optimized to avoid (b) (4) (b) (4) (b) (4).

Based on the pharmaceutical development program described above for Oravig, two formulations were prepared for clinical trials evaluation containing 50 mg and 100 mg of miconazole. Their compositions are described in the table below.

Table 3.2.P.2-11 Composition of Miconazole Lauriad® MBT, Clinical Trial Batches

Component	Drug Product Strength		% (w/w)
	50 mg	100 mg	
Miconazole	50.00	100.00	43.48
Hypromellose (b) (4)			(b) (4)
MPC			
Maize Starch			
Lactose Monohydrate			
SLS			
Magnesium Stearate			
Talc			
			(b) (4)
Total	115.00	230.00	100.0

(b) (4)

2.2. General Clinical Pharmacology

What are the design features of the clinical trials?

The Oravig clinical development program consisted of 4 clinical studies comprising 1 Phase 1 study in healthy volunteers (BA2000/01/01) and 3 Phase 3 studies in immunocompromised patients; one pivotal trial in HIV-positive patients (BA2002/01/03) and two supportive trials, one in HIV-positive patients and another in head and neck cancer patients (BA2004/01/04 and BA2002/01/02, respectively).

The Phase 1 study was designed to obtain the pharmacokinetic profile of Oravig in saliva and plasma from healthy volunteers, and to evaluate the tolerability and acceptability of Oravig. Three Phase 3 clinical studies were designed to determine efficacy and safety and to obtain data in a representative sample of the most severe populations suffering from OPC, allowing the data to be safely generalized to all patients with OPC.

What is the available pharmacokinetic information?

In the Phase 1 PK Study BA2000/01/01 in healthy volunteers, median Tmax occurred 6 to 7 hours after the application of Oravig 50 mg and 100 mg. This was consistent with the *in vitro* dissolution tests that showed a similar profile between the 50 and 100 mg tablets, with up to 80% of miconazole dissolution by 8 hours. These results suggest that the rate of release of miconazole from Oravig is not dependent on tablet strength and support the once-daily dose regimen as well as the recommendation to apply a second Oravig tablet in case of dislodgement within 6 hours after application.

Cmax and AUC were approximately linear between the 50 and 100 mg doses. Cmax and AUC values were at least 10 fold higher than those observed after administration of miconazole 125 mg oral gel.

Study BA2000/01/01

	BA001- 50	BA001- 100	Gel
C_{max} (µg/mL)			
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Standard deviation	16.21	49.29	1.62
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AUC (0-12) (µg.h/mL)			
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Standard deviation	35.09	149.54	6.49
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CV (%)	63.54	109.82	152.07
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50 vs 100	*p=0.01*		

The mean duration of miconazole saliva concentrations >1.0 µg/mL (The MIC90 value for *C. albicans* and most non-*albicans* species involved in OPC) was 13.3 ± 5.2 and 14.4 ± 7.9 hours after application for the 50 and 100 mg Oravig doses, respectively; the difference between the 2

doses was not significant. For both Oravig strengths, the duration of this concentration was significantly longer ($P<.001$) than the 1.2 ± 2.6 hours observed after the administration of miconazole 125 mg oral gel. Saliva concentrations >1.0 μg/mL were reached within 1 hour after tablet application with both Oravig 50 mg and 100 mg.

Interestingly, in some subjects, significant miconazole concentrations were still detected in saliva several hours after tablet detachment. Therefore, in patients with the shortest adhesion times, mean total exposure to miconazole concentrations >1.0μg/mL in saliva was always more than 9 hours except in one patient (5.8 hours), confirming that even when adhesion of the tablet to the gum is short, miconazole concentrations in saliva reach the MIC90 values of *Candida* for a clinically relevant duration.

Miconazole was detected in 9 of 324 (2.7%) plasma samples from a small number (n = 7) of subjects after the application of Oravig 50 and 100 mg. Measurable plasma concentrations ranged from 0.41 to 0.83 μg/mL (LLOQ = 0.4 μg/mL). The number of samples containing measurable amounts of miconazole in plasma was comparable between the 2 strengths of Oravig (5 and 4 samples for the 50 and 100 mg Oravig, respectively) and was almost half as common as with oral gel treatment. The systemic exposure to miconazole was also evaluated in 40 HIV-positive patients treated with Oravig 50 mg once-daily multiple doses. Miconazole plasma concentrations were not detected in any of samples obtained after 7 days of Oravig 50 mg treatment (Day 7).

These data confirmed low systemic absorption of miconazole through the buccal mucosa or the gastrointestinal tract after swallowing saliva following the application of Oravig 50 mg.

What are the characteristics of the dose-response relationships for efficacy?

There is no dose-response (PK/PD) clinical study conducted to establish the dose-response relationship for efficacy.

Three Phase 3 studies were conducted in a total of 896 patients who were markedly immunocompromised as well as in those with critical oral conditions to analyze the efficacy and safety of Oravig 50mg as compared with the currently prescribed treatments (miconazole 125mg oral gel and clotrimazole 10mg troche) as comparators.

The following table lists the summary of efficacy data in the Phase 3 studies with Oravig 50mg once daily, miconazole 125 mg oral gel 4 times daily, and clotrimazole 10mg troche 5 times per day for 14 days.

Study ID No. Patient Pop	Treatment Groups	Patients Enrolled/ Completed	Primary End Points (ITT)		Secondary End Points (ITT)			
			CC Day 15 n (%)	CR + PR Day 15 n (%)	CR Day 15 n (%)	CR + PR Day 8 n (%)	Relapse Rate n (%)	Mycological Cure n (%)
BA2004/01/04[a] HIV-positive	Miconazole Lauriad® 50 mg MBT once daily	291/290	**176/290 (60.7%)**	203/290 (70.0%)	189/290 (65.2%)	121/290 (41.7%)	51/183 (27.9%) 21 d post treatment	79/290 (27.2%)
	Clotrimazole 10 mg troche 5 times/day	287/287	**187/287 (65.2%)** **(95% CI, -0.124 to 0.034)**	207/287 (72.1%)	198/287 (69.0%)	107/287 (37.3%)	53/197 (26.9%) 21 d post treatment	71/287 (24.7%)
BA2002/01/03 HIV-positive	Miconazole Lauriad® 50 mg MBT once daily	26/25	13/25 (52.0%)	**21/25 (84.0%)**	13/25 (52.0%)	20/25 (80.0%)	8/25 (32.0%) 30 d post treatment	7/25 (28.0%)
BA2002/01/02 Head and Neck Cancer	Miconazole Lauriad® 50 mg MBT once daily	153/141	55/141 (39.0%)	**79/141 (56.0%)**	74/141 (52.5%)	20/141 (14.2%)	16/74 (21.6%) 45 d post treatment	64/141 (45.4%)
	Miconazole 125 mg oral gel 4 times/day	153/141	55/141 (39.0%)	**69/141 (48.9%)** **(95% CI, -0.048 to 0.19)**	64/141 (45.4%)	28/138 (20.3%)	11/64 (17.2%) 45 d post treatment	77/141 (54.6%)

[a]In this trial, endpoints were evaluated 3 to 8 days following treatment discontinuation CC indicates clinical cure; CR, complete response (oral signs); OD, once daily; CI, confidence interval; and PR, partial response (oral signs). Bolded boxes show the primary endpoints as specified in the individual trials.

What are the safety issues attributed to Oravig 50mg treatment?

The applicant reported that the majority of application site reactions were transient and self-limited. Pain was commonly observed on the day of Oravig treatment and usually resolved after tablet removal.

Treatment-emergent adverse events (TEAEs) were reported in more than 3% of patients: gastrointestinal events (18.1%), infections and infestations (7.6%), nervous system (7.5%), general disorders and administration site conditions (4.7%), respiratory, thoracic and mediastinal disorders (3.3%), and blood and lymphatic system disorders (3.2%).

The following table lists the treatment-emergent adverse reaction incidences from the Phase 3 clinical trials.

Preferred Term	Miconazole Lauriad® 50 mg MBT Once daily (n = 462)	Clotrimazole 10 mg troches 5 times/day (n = 287)	Miconazole 125 mg OG 4 times/day (n = 147)	Total (N = 896)
Adverse events	339	318	38	721
Patients ≥1 TEAE	154 (33.3%)	128 (44.6%)	32 (21.8%)	314 (35.0%)
Headache	21 (4.5%)	19 (6.6%)	1 (0.7%)	41 (4.6%)
Nausea	20 (4.3%)	22 (7.7%)	2 (1.4%)	44 (4.9%)
Diarrhea	18 (3.9%)	22 (7.7%)	1 (0.7%)	41 (4.6%)
Dysgeusia	11 (2.4%)	3 (1.0%)	0 (0.0%)	14 (1.6%)
Abdominal upper pain	9 (1.9%)	8 (2.8%)	3 (2.0%)	20 (2.2%)
Vomiting	8 (1.7%)	9 (3.1%)	3 (2.0%)	20 (2.2%)
Dry mouth	7 (1.5%)	5 (1.7%)	0 (0.0%)	12 (1.3%)
Ageusia	7 (1.5%)	1 (0.3%)	1 (0.7%)	9 (1.0%)
Pruritus	6 (1.3%)	1 (0.3%)	0 (0.0%)	7 (0.8%)
Abdominal pain	6 (1.3%)	6 (2.1%)	0 (0.0%)	12 (1.3%)
Oral discomfort	6 (1.3%)	1 (0.3%)	2 (1.4%)	9 (1.0%)
Gingival pain	6 (1.3%)	2 (0.7%)	0 (0.0%)	8 (0.9%)
Fatigue	5 (1.1%)	6 (2.1%)	0 (0.0%)	11 (1.2%)
Back pain	5 (1.1%)	5 (1.7%)	0 (0.0%)	10 (1.1%)
Upper RTI	5 (1.1%)	5 (1.7%)	0 (0.0%)	10 (1.1%)
Rash	5 (1.1%)	1 (0.3%)	0 (0.0%)	6 (0.7%)
Gastroenteritis	2 (0.4%)	8 (2.8%)	0 (0.0%)	10 (1.1%)
Pharyngolaryngeal pain	1 (0.2%)	7 (2.4%)	0 (0.0%)	8 (0.9%)
Pain	3 (0.6%)	7 (2.4%)	0 (0.0%)	10 (1.1%)
Toothache	1 (0.2%)	4 (1.4%)	1 (0.7%)	6 (0.7%)
Anorexia	4 (0.9%)	4 (1.4%)	0 (0.0%)	8 (0.9%)
Pruritus generalized	3 (0.6%)	4 (1.4%)	0 (0.0%)	7 (0.8%)
Anemia	3 (0.6%)	4 (1.4%)	0 (0.0%)	7 (0.8%)
Neutropenia	2 (0.4%)	4 (1.4%)	0 (0.0%)	6 (0.7%)
Lymphadenopathy	2 (0.4%)	4 (1.4%)	0 (0.0%)	6 (0.7%)
Chest pain	1 (0.2%)	4 (1.4%)	0 (0.0%)	5 (0.6%)
Pneumonia	0 (0.0%)	4 (1.4%)	0 (0.0%)	4 (4.0%)
Dyspepsia	2 (0.4%)	3 (1.0%)	1 (0.7%)	6 (0.7%)
Cough	4 (0.9%)	3 (1.0%)	0 (0.0%)	7 (0.8%)
Pyrexia	2 (0.4%)	3 (1.0%)	0 (0.0%)	5 (0.6%)
Application site irritation	4 (0.9%)	1 (0.3%)	3 (2.0%)	8 (0.9%)
Glossodynia	4 (0.9%)	1 (0.3%)	3 (2.0%)	8 (0.9%)

MBT indicates Mucoadhesive buccal tablet; OG, Oral gel; TEAE, Treatment emergent adverse event; and RTI, Respiratory tract infection.

2.3. Intrinsic & Extrinsic Factors

Are there any significant intrinsic or extrinsic factors that affect the PK of Oravig?

There were no studies in patients with renal impairment, hepatic impairment, or elderly subjects conducted with Oravig. Since the pharmacokinetic study (BA 2000/01/01) confirmed the absence or the low systemic absorption of miconazole from Oravig, a dosage adjustment in patients with renal or hepatic impairments will not be necessary.

No formal drug interaction studies have been performed with Oravig. Although miconazole is a known inhibitor of CYP2C9 and CYP3A4, the potential for drug-drug interactions will be minimal with the low miconazole systemic exposure.

2.4. Analytical Section

What bioanalytical methods are used to assess miconazole concentrations?

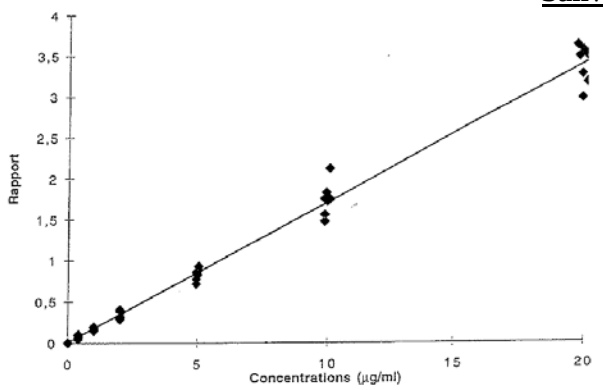
The High Performance Liquid Chromatography (HPLC) assay method chosen allows determination of the quantities of miconazole present in samples of plasma and saliva. The principle of the assay is as follows: after protein precipitation with acetonitrile and addition of (b) (4) as internal standard, followed by centrifugation, the supernatants are analyzed by HPLC with ultraviolet detection.

What is the range of the standard curve? What curve fitting techniques are used?

A range of standard concentrations of the substance to be examined in the saliva and plasma was assayed on several consecutive days. This protocol was used to investigate the linearity of the assay method. A standard range consisting of 7 concentrations (0, 0.4, 1, 2, 5, 10, 20 µg/mL) was obtained by adding solutions of miconazole. Each time the range included one point for which no test compound was added.

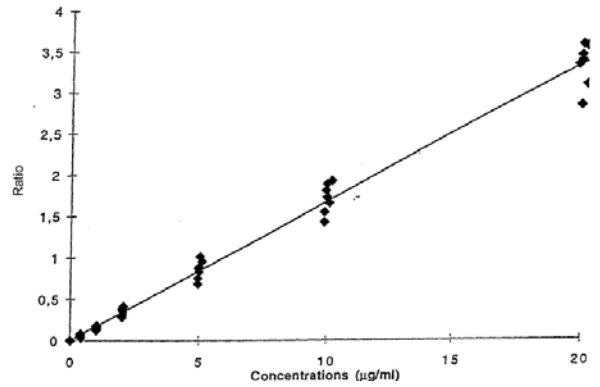
The data were fitted to a straight line of type y = ax + b where "a" is the slope and "b" is the y intercept. The determination coefficient (r2) was calculated. The straight line was calculated by the method of least squares. The regression line and the parameters were following.

Saliva



Straight line parameters	
Number of ranges	7
Slope	0.16928
y intercept	0.0064
r	0.9944
r2	0.9888

Plasma



Straight line parameters	
Number of ranges	7
Slope	0.16712
y intercept	0.0027
r	0.9938
r2	0.9876

What are the limit of detection and the lower limit of quantification?

The limit of detection and the lower limit of quantification both in the saliva and in the plasma were found to be 0.2 µg/mL and 0.4 µg/mL, respectively. The assay has satisfactory linearity.

What are the repeatability and specificity?

The repeatability was determined by injecting the same pure solution of the test substance at miconazole concentration of 4 µg /mL and the internal standard onto the column 6 times. The relative standard deviation of the peak AUC was less than 2% both in the saliva and in the plasma, which complies the chromatographic system repeatability.

The specificity of the method was verified by checking that the solvent, saliva or plasma, and collecting tubes do not interfere with miconazole and internal standard.

What is the QC sample assessed, and what are the accuracy and precision of the QC sample concentrations?

Quality controls were carried out from the start of the assays, in accordance with the instructions given in GLP techniques. The precision (%CV) and accuracy (%Error) were determined using three different salivary or plasma concentrations: 1, 5 and 10 µg of miconazole per ml were prepared, and then assayed at T0. For each concentration, 6 different extractions were carried out using the same stock solution of miconazole.

Saliva

	True concentration (µg/ml)	Calculated concentration (µg/ml)	Mean calc. concentration (µg/ml)	Precision (%)
	(b) (4)			
LOW CONCENTRATION		0.92 0.91 0.98 1.15 0.89 1.03	0.98 ± 0.098	10.0
INTERMEDIATE CONCENTRATION		4.79 4.7 4.65 4.71 4.79 4.99	4.77 ± 0.12	2.5
HIGH CONCENTRATION		10.29 10.3 9.72 10.23 10.43 10.44	10.24 ± 0.27	2.6

	True concentration (µg/ml)	Calculated concentration (µg/ml)	Mean calc. concentration (µg/ml)	Accuracy (%)
LOW CONCENTRATION	(b) (4)	0.92 0.91 0.98 1.15 0.89 1.03	0.98 ± 0.098	-1.01
INTERMEDIATE CONCENTRATION		4.79 4.7 4.65 4.71 4.79 4.99	4.77 ± 0.12	-3.6
HIGH CONCENTRATION		10.29 10.3 9.72 10.23 10.43 10.44	10.24 ± 0.27	3.4

Plasma

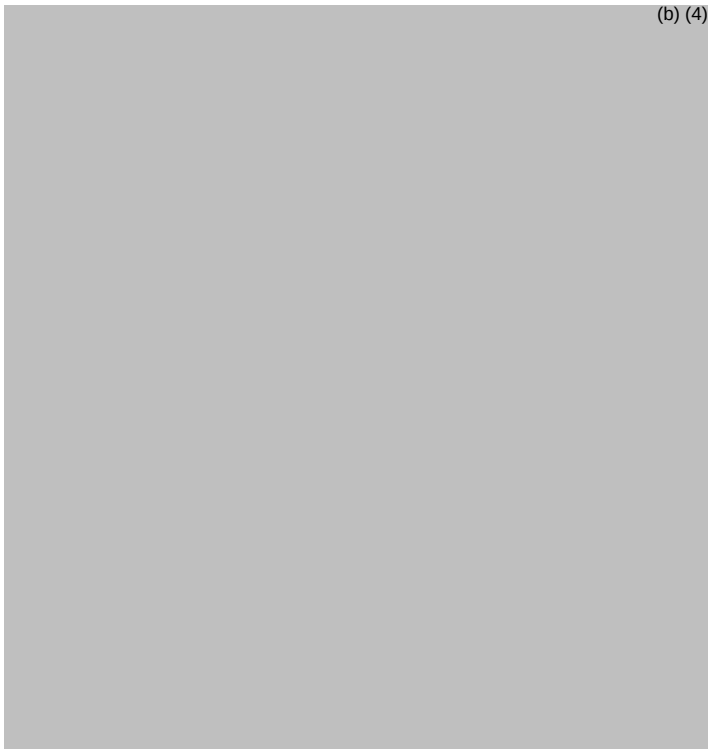
	True concentration (µg/ml)	Calculated concentration (µg/ml)	Mean calc. concentration (µg/ml)	Precision (%)
LOW CONCENTRATION	(b) (4)	1.01 0.89 1.1 1.03 1.1 1.21	1.06 ± 0.108	10.2
INTERMEDIATE CONCENTRATION		4.87 5.1 4.81 4.82 5.02 4.98	4.93 ± 0.12	2.4
HIGH CONCENTRATION		10.65 10.13 10.02 10.02 9.58 10.29	10.12 ± 0.35	3.5

	True concentration (µg/ml)	Calculated concentration (µg/ml)	Mean calc. concentration (µg/ml)	Accuracy (%)
LOW CONCENTRATION	(b) (4)	1.01 0.89 1.1 1.03 1.1 1.21	1.06 ± 0.108	5.67
INTERMEDIATE CONCENTRATION		4.87 5.1 4.81 4.82 5.02 4.98	4.93 ± 0.12	-1.3
HIGH CONCENTRATION		10.65 10.13 10.02 10.02 9.58 10.29	10.12 ± 0.35	1.2

What is the sample stability after 24 hours at room temperature or after storing in a freezer until required for analysis?

The extracted saliva or plasma sample displayed good stability after 24 hours at room temperature protected from light.

The stability of plasma samples stored in the freezer displayed no evidence of any problem. However, the concentrations of the frozen salivary samples tended to fall. This was due to the poor solubility of the active substance which, after the sample had been thawed, re-dissolved to a limited extent only and in an irregular manner, although the values did tend to stabilize after some time. After adding the (b) (4) which is present in the tablet formulation ((b) (4) sodium lauryl sulphate), the (b) (4) (b) (4) that can then be extracted without causing too many problems for the assay. Wide variation in the stability study was observed.



What is the cross-validation evaluated?

Cross-validation was conducted by analyzing a standard range of concentrations in parallel using two different HPLC systems, and there were no differences between the results obtained with the two different HPLC systems.

12 pages of draft labeling has been withheld as B(4) CCI/TS immediately following this page

4.2. Individual Study Review

Phase 1 Trial:

Study No. BA2000/01/01:
Title: **Pharmacokinetic and Tolerability Study of Single Administraiton of Oravig at Two Dosages (50 or 100 mg) in Comparison with Miconazole Buccal Gel in 18 Healthy Volunteers**

Objective
To determine the pharmacokinetics parameters of miconazole in the saliva and plasma of healthy volunteers, following administration of single Oravig containing 50 mg and 100 mg miconazole compared with miconazole oral gel 125 mg three times per day (total 375 mg). To evaluate the clinical tolerability and acceptability of Oravig.

Methods
A single center, randomized, open-label, three treatment cross-over study was performed in healthy volunteers to assess the pharmacokinetics of miconazole in saliva and plasma following administration of single Oravig containing 50, 100mg miconazole or three applications buccal gel containing miconazole 125mg (Daktarin® gel). 18 healthy volunteers (18 to 35 years old, 9 males, 9 females) were enrolled. Subjects were randomized to receive the three study medications in a different order. All eighteen subjects completed three cross-over phases. The washout period between treatments was one week, and for each volunteer, all three treatments were administered on the same day of each week.

	Subjects
No. of Subjects and Gender	9 males, 9 females
Mean Age (range)	23 years old (19 to 29 years old)
Mean Body Weight (range)	66.9 kg (47 to 94 kg)
Mean Height (range)	174 cm (163 to187 cm)

A single Oravig was inserted at T 0 h either with the fingers or a by means of a disposable device allowing centering of the tablet in the cuspid fossa and facilitating its adherence. After buccal administration, the tablet remained in the oral cavity until its complete erosion or its loss of adhesion. Three buccal applications of 125 mg (2 measure-spoonsful) were made at T 0 h, T 3.5 h and T 8.5 h: the gel had to be kept in the mouth for as long as possible (2 to 3 minutes) before being swallowed.

Salivary samples were taken before administration of miconazole and at 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 and 24 Hours post dose. Venous blood was collected before drug administration and at 0.5, 1, 2, 3, 4, 8, 12, and 24 hours post dose. Pharmacokinetic parameters in saliva and plasma samples were assessed by using a High- Performance Liquid Chromatography (HPLC) technique (LLOQ was 0.4 µg/mL).

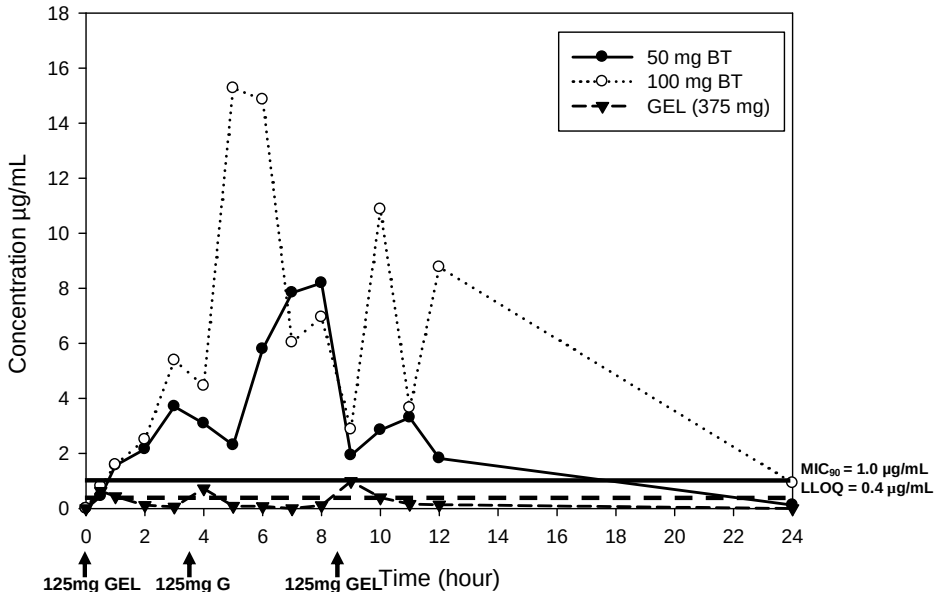
The pharmacokinetic parameters determined were Cmax, Tmax, AUC (0-12h), and AUC (0-24h). Additionally, two other parameters were also calculated. The mean duration of miconazole concentration above 1.0 µg/mL, which is the cut off of the minimum inhibitory concentration of miconazole. Time to tablet erosion or detachment was recorded. Assessment of tolerability was based on adverse event reporting, local (buccal) examination and patient questionnaire. Assessment of adhesion and acceptability were also based on a patient questionnaire.

Results

The exposure, in terms of AUCs achieved with the 50 mg tablet, was approximately half that achieved with the 100 mg tablet and at least 10 times higher than that of the gel formulation. The tablets gave a single peak concentration at 6 or 7 h after application, and statistically, the salivary AUCs and Cmax values obtained after administration of the tablets were significantly higher ($P < 0.0001$) than those obtained after administration of the gel. Significant differences were also observed ($P = 0.01$) between the two dosages of tablet for both Cmax and AUC(0-24 h). Plasma AUC, Cmax and Tmax were not calculated due to insufficient data above LLOQ.

The pharmacokinetic parameters observed for the two doses are presented in the following graphs and tables.

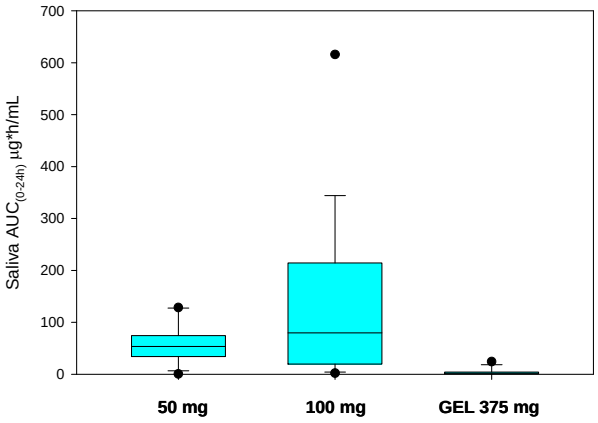
Mean Concentration of Miconazole in Saliva



Interindividual variability was high, with one subject having extremely low miconazole salivary concentrations at both tablets doses and one subject with detectable miconazole concentrations only 12 h after the 50 mg dose. The lowest interindividual variability was observed after the 50 mg tablet. A coefficient of variation of 111% for AUC(0-24 h) was obtained after the 100 mg dose compared with 64% after 50 mg.

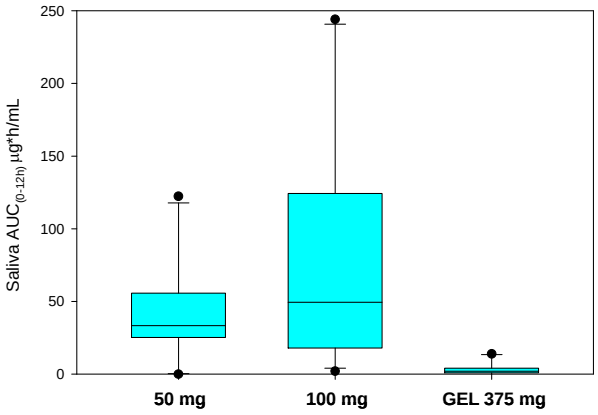
Pharmacokinetics of miconazole in Saliva

$AUC_{(0\text{-}24h)}$ of Miconazole in Saliva



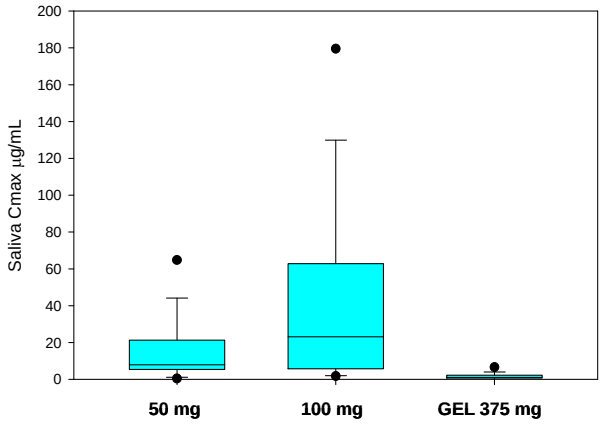
Saliva Miconazole AUC(0-24h) (µg*h/mL)					
	# Subjects	Mean (95% CI)	Range	SD	CV(%)
50 mg BT	18	55.14 (6.19 - 127.44)	(0.45 - 128.3)	35.1	63.66
100 mg BT	18	136.40 (3.92 - 359.19)	(2.01 - 615.6)	151.18	110.84
GEL	18	4.25 (0 - 18.71)	(0 - 24.4)	6.49	152.71
50 vs 100	*p=0.033*				
50 vs GEL	*p<0.0001*				
100 vs GEL	*p=0.0007*				

$AUC_{(0\text{-}12h)}$ of Miconazole in Saliva



Saliva Miconazole AUC (0-12h) (µg*h/mL)					
	# Subjects	Mean (95% CI)	Range	SD	CV(%)
50 mg BT	18	43.47 (0.38 - 118.09)	(0 - 122.3)	33.2	76.37
100 mg BT	18	78.62 (3.92 - 240.93)	(2.01 - 244)	78.42	99.75
GEL	18	3.43 (0 - 13.43)	(0 - 13.87)	4.14	120.7
50 vs 100	*p=0.0889*				
50 vs GEL	*p<0.0001*				
100 vs GEL	*p=0.0003*				

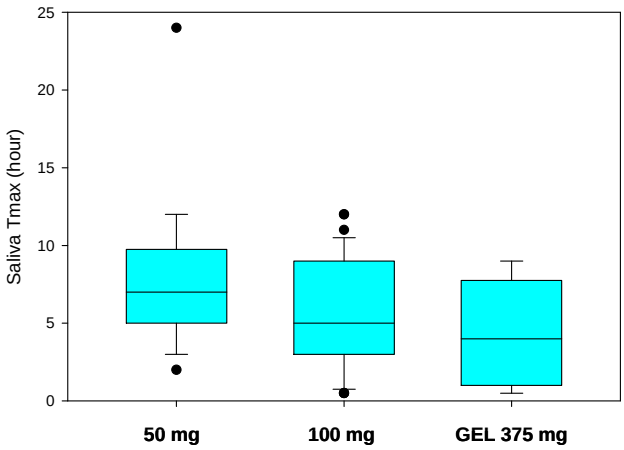
Cmax in Saliva



Saliva Miconazole Cmax (µg/mL)

	# Subjects	Mean (95% CI)	Range	SD	CV(%)
50 mg BT	18	15.07 (1.09 - 45.27)	(0.45 - 64.75)	16.21	107.56
100 mg BT	18	39.05 (1.97 - 132.63)	(1.72 - 179.5)	49.29	126.22
GEL	18	1.61 (0 - 4.11)	(0 - 6.59)	1.62	100.62
50 vs 100	*p=0.0581*				
50 vs GEL	*p=0.0013*				
100 vs GEL	*p=0.0028*				

Tmax in Saliva

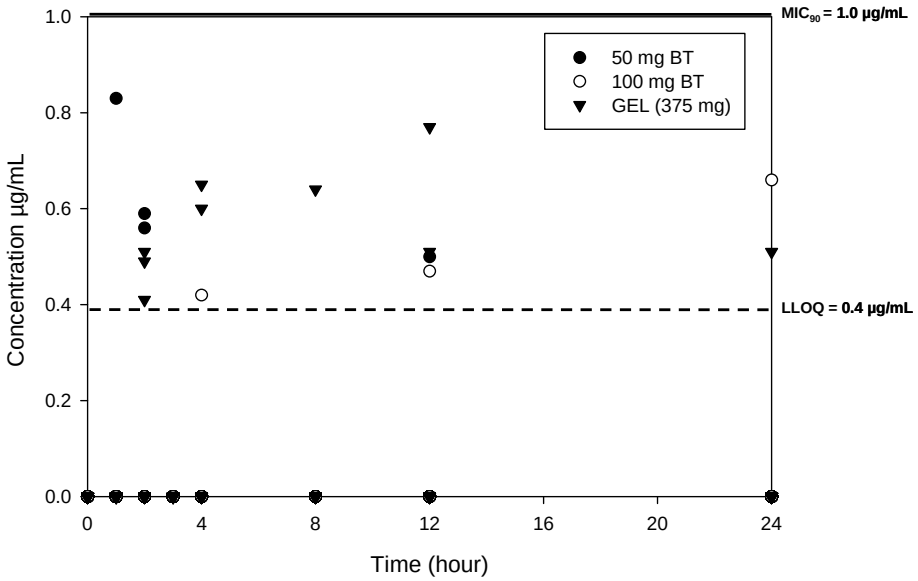


Saliva Miconazole Tmax (hour)

	# Subjects	Median (95% CI)	Range	SD	CV(%)
50 mg BT	18	7 (2.85 - 13.8)	(2 - 24)	4.85	60.63
100 mg BT	18	6 (3 - 12)	(3 -12)	3.04	43.8
GEL	16	4 (0.5 - 9)	(0.5 - 9)	3.39	88.28
50 vs 100	*p=0.4394*				

Miconazole concentrations were below the lower limit of quantification in plasma at most time points. Miconazole was detected in 9 of 324 (2.7%) plasma samples from a small number (n = 7) of subjects after the application of Oravig 50 and 100 mg. Measurable plasma concentrations ranged from 0.41 to 0.83 µg/mL (LLOQ = 0.4 µg/mL). The number of samples containing measurable amounts of miconazole in plasma was comparable between the 2 strengths of Oravig (5 and 4 samples for the 50 and 100 mg Oravig, respectively) and was almost half as common as with oral gel treatment. The gel, which gave lower salivary concentrations, led to measureable plasma concentrations more frequently than the tablets, probably due to swallowing of the gel and the higher dosage.

Concentration of Miconazole in Plasma



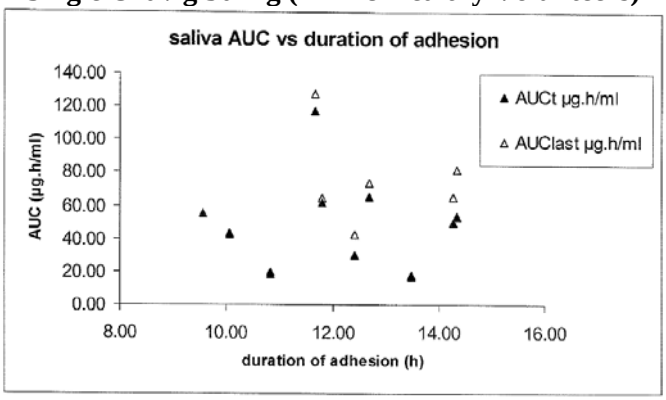
The mean duration of adhesion was 15 hours for both dosages of Oravig, with a minimum duration of 9.6 hours for the 50 mg tablet and 4.7 hours for the 100 mg tablet. Maximum adhesion duration time with both tablets was 24.2 hours. The end of adhesion was secondary to tablet detachment on 2 occasions for the 50 mg tablet and 7 for the 100 mg tablet.

Duration of adhesion (hour) (N = 18 Healthy Volunteers)

	BA001-50	BA001-100
Mean	15.2	15.1
Standard-deviation	4.4	6.7
Minimum	9.6	4.8
Maximum	24.2	24.2

There was no correlation between the duration of adhesion and saliva miconazole exposure. The mean duration of miconazole saliva concentrations >1.0 µg/mL was 13.3 ± 5.2 and 14.4 ± 7.9 hours after application for the 50 and 100 mg Oravig doses, respectively; the difference between the 2 doses was not significant. Saliva concentrations >1.0 µg/mL were reached within 1 hour after tablet application with both Oravig 50 mg and 100 mg.

Single Oravig 50 mg (N = 18 Healthy Volunteers)



No adverse event was reported for the 50 mg tablet. Six adverse events were reported by 5 of the 18 trial subjects, with 4 adverse events considered as probably related to the study drug. The most common adverse event was buccal irritation (n = 3), which was classified as mild in severity. The clinical examination performed after the administration of each study medication revealed no localized buccal abnormality associated with any of the study medications.

Reported Adverse Events

	BA001-50	BA001-100	GEL
Abdominal disorder	-	-	1*
Headache	-	1	1
Buccal/lips irritation	-	2	1
Total	0	3	3

* Reported twice on the same day.

For 16 of the 18 subjects, the preferred formulation was the 50 mg Oravig. The 100 mg Oravig was preferred by one of the 18 subjects and the gel was also preferred by one of the 18 subject. One subject noted a bad taste for the 50 mg tablet compared with 13 for the gel. Discomfort with the 100 mg tablet was essentially due to its size.

Questionnaire on local tolerability (oral confort, taste, tablet size, etc)

	BA001-50	BA001-100	GEL
Highly acceptable	15	6	2
Acceptable	3	4	2
Moderately acceptable	0	8	7
Unacceptable	0	0	7

Conclusion

This pharmacokinetic study in 18 healthy volunteers demonstrated that the proposed dose (50 mg) Oravig administered once a day was a system permitting a sustained release of miconazole into the saliva in concentrations higher than those released from the commercial gel formulation (Daktarin®). The parameters evaluated in this study including salivary exposure to miconazole, adhesion time, and acceptability displayed that the 50 mg tablet appeared to be an appropriate dose for the Phase III clinical development program.

Phase 3 Trials:

Study No. BA2004/01/04 (SMiLES):

Title: **A Comparative Randomized, Double-Blind, Double-Dummy, Multicenter Study of the Efficacy and Safety of Oravig 50 mg Administered Once a Day and Mycelex® Troches (Clotrimazole 10 mg) Administered Five Times a Day in the Treatment of Oropharyngeal Candidiasis in Immunocompromised Patients**

Objective
To determine whether the clinical cure rate of Oravig 50 mg applied once daily for 14 days was not inferior to that of clotrimazole 10 mg troche administered 5 times per day (total daily dose of 50 mg) for 14 days.

Methods
697 patients (18 to 73 years old) were randomized 1:1 to receive one 14 day treatment course of either "active Oravig 50 mg tablet once daily and placebo troche 5 times per day" or "placebo buccal tablet once daily and active clotrimazole troche 5 times per day".

The blood samples from 20 patients, regardless of the enrollment site, were drawn at Day 7, 6 to 8 hours after the Oravig 50 mg application, and the plasma concentrations were measured by HPLC method (LLOQ = 0.1 μg/mL). The duration of adhesion and the mean percentage compliance values were evaluated in both the treatment groups.

Results
Miconazole plasma concentrations were not detected in any of the 20 HIV-positive patients tested (LLOQ = 0.1 μg/mL) after 7 doses of Oravig 50 mg (Day 7).

Of the 3983 Oravig 50 mg applied, 3617 (90.8%) adhered for at least 6 hours, 2641 (66.3%) for at least 12 hours and 1797 (45.1%) were still adhering at bedtime. Respective adherence figures for the 3863 placebo buccal tablets applied in the clotrimazole group, were 3538 (91.6%), 2752 (71.2%) and 1917 (49.6%). Very few Oravig 50 mg (6.3%) dislodged in the first 6 hours and 216 out of 249 were replaced. There were no major safety issues in either treatment group.

Summary of Adhesion, by Treatment Group

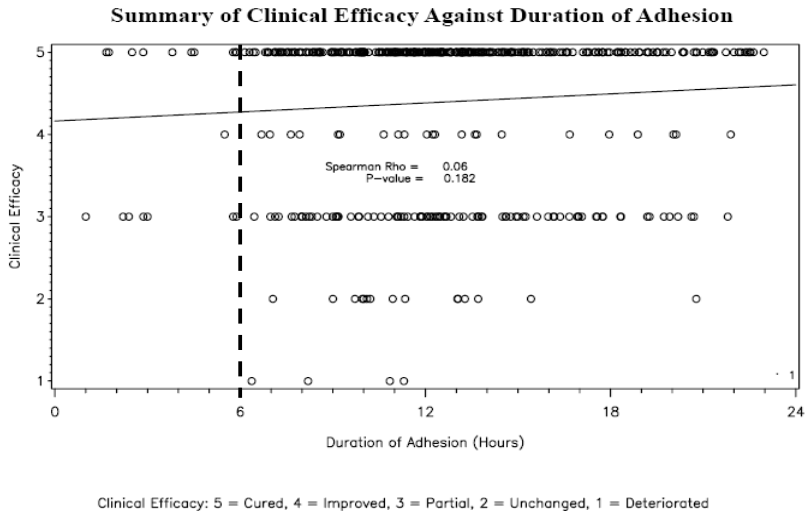
	Treatment Group	
Parameter	Miconazole Lauriad® MBT 50 mg (N=290)	Clotrimazole Troches 10 mg (N=287)[a]
Total number of MBT applied	3983	3863
Mean duration of adhesion (hour : minute)	12:37	13:10
Total number and percent of MBT adhered to at least 6 hours, N (%)	3617 (90.8%)	3538 (91.6%)
Total number and percent of MBT adhered to at least 12 hours, N (%)	2641 (66.3%)	2752 (71.2%)
Total number and percent of MBT adhered to just before the bed time, N (%)	1797 (45.1%)	1917 (49.6%)
Total number and percent of MBT detached within the first 6 hours after placement, N (%)	249 (6.3%)	219 (5.7%)
Total number of MBT replaced	216	216

Source: Table 14.3.15

N=number of patients, MBT=mucoadhesive buccal tablet

[a] Adhesion of placebo buccal tablets

The correlation between clinical efficacy and duration of adhesion was very low (p=0.182) and was not found to be statistically significant.



The mean duration of adhesion was comparable in both the treatment groups (12 hours and 37 minutes for the miconazole group and 13 hours and 10 minutes for the clotrimazole group [placebo buccal tablets]). There were an equal number of tablets (216 tablets) replaced in both treatment groups. The number of tablets detached was higher in the miconazole group (249 [6.3%]) than in the clotrimazole group (219 [5.7%]).

The mean percentage compliance values were approximately 97% and 95% in the miconazole group and the placebo group respectively over 14 days.

Conclusion
Miconazole plasma concentrations were not detected in any of the 20 HIV-positive patients tested (LLOQ = 0.1 µg/mL) after 7 doses of Oravig 50 mg (Day 7). The adhering times after the Oravig 50 mg application in HIV-positive patients were not significantly different from that observed in healthy volunteers in Study BA2000/01/01. The correlation between clinical efficacy and duration of adhesion was very low.

Study No. BA2002/01/03 :

Title: **Open Non-Comparative Phase III Trial Evaluating the Anti-Fungal Activity and Tolerance of Oravig in the Treatment of Oropharyngeal *Candiasis* in HIV-Positive Patients**

Objective
To evaluate the efficacy and safety of a 14-day treatment with Oravig 50 mg in HIV-positive patients suffering from OPC.

Methods
26 patients (20 to 75 years old) were enrolled, and Oravig 50 mg was administered once daily in the morning for 14 days. Blood samples were drawn at day 7 in 20 patients. The plasma concentrations were measured by HPLC method (LLOQ = 0.1 µg/mL). The duration of adhesion and the mean percentage compliance values were evaluated in both the ITT and PP populations.

Results
The trial was halted by the expert committee after the first interim analysis due to a higher than expected efficacy rate according to the predefined rules.

Miconazole plasma concentrations were not detected in any of the HIV-positive patients tested (LLOQ = 0.1 μg/mL).

The following table displays the number and percentage of tablets still adhering 6 hours post dosing, 12 hours post dosing and at bedtime.

	ITT*	PP*
Number of tablets adhering 6 hours post dosing (%)	223/242 (92.1%)	174/187 (93.0%)
Number of tablets adhering 12 hours post dosing (%)	145/258 (56.2%)	119/203 (58.6%)
Number of tablets adhering at bedtime (%)	97/256 (37.9%)	85/202 (42.1%)

* Note: a total number of 311 and 246 tablets were taken by the ITT and PP populations [53 (17%) and 43 (21%) missing data respectively at 12 hours]
See Table 20 in Appendix 16.2.5 and Listing 22 in Appendix 16.4.1.

20 out of 25 patients (80%) of the ITT population and 14 out of 19 patients (73.7%) of the PP population had a compliance value ≥80% during the study.

Conclusion
Miconazole plasma concentrations were not detected in any of the HIV-positive patients after 7 doses of Oravig 50 mg (Day 7) (LLOQ = 0.1 μg/mL). The adhering times after the Oravig 50 mg application in both the ITT and PP populations were not significantly different from that observed in healthy volunteers in Study BA2000/01/01.

Study No. BA2002/01/02 :

Title: Comparision of the Efficacy and Safety of Oravig to those of Miconazole Gel in the Treatment of Oropharyngeal Candidiasis: A Multicenter Randomized Phase III Trial in Patients Treated with Radiotherapy for Head and Neck Cancer

Objective
To determine whether the efficacy of Oravig 50 mg administered once daily for 14 days was not inferior to that of miconazole 125 mg oral gel administered 4 times per day for 14 days.

Methods
This trial was conducted according to an open, randomized, comparative, 2 parallel arms design. 306 patients (17 to 83 years old) were enrolled in the study and were randomized 1:1 to receive either Oravig 50 mg or miconazole 125 mg oral gel. Oravig 50 mg was administered once daily in the morning for 14 days, and miconazole 125 mg oral gel was administered 4 times per day (total daily dose of 500 mg) for 14 days. The duration of adhesion was evaluated in both the mITT and PP populations.

Results
The mITT and PP populations comprised 282 and 213 patients, respectively. There were no demographical differences between the two groups at baseline. Salivary flow was dramatically

reduced in 96% of patients compared with the salivary flow in healthy volunteers and even absent in 20% of patients.

The following table displays the number and percentage of tablets still adhering 6 hours post dosing, 12 hours post dosing and at bedtime.

	mITT*	PP*
Number of tablets adhering 6 hours post dosing (%)	1362/1499 (90.8%)	1044/1132 (92.22%)
Number of tablets adhering 12 hours post dosing (%)	1029/1762 (58.39%)	831/1350 (61.6%)
Number of tablets adhering at bedtime (%)	788/1701 (46.32%)	649/1309 (49.57%)

* note: a total number of 1829 tablets were taken by the mITT [330 (18.04%), 67 (3.66%) and 128 (7%) missing data respectively at 6, 12 hours and bedtime]. and 1398 in the PP population [266 (19.03%),48 (3.43%) and 89 (6.36%) missing data respectively at 6, 12 hours and bedtime)]
(See also Tables 14.4.1.1, 14.4.1.5, 14.4.1.6, 14.4.1.7, 14.4.1.11 and 14.4.1.12).

Conclusion
The adhering times after the Oravig 50 mg application in cancer patients with reduced salivary flow were not significantly different from the adhering times observed in healthy volunteers and in HIV-positive patients.

Reviewer discussion:
Oravig 50 mg displayed miconazole saliva concentrations higher and longer than those obtained with miconazole 125 mg oral gel. While C_{max}, AUC $_{0\text{-}12h}$ and AUC $_{0\text{-}24h}$ in saliva were approximately dose proportional between Oravig 50 mg to Oravig 100 mg, the durations of exposure to the concentration over MIC_{90} were not significantly different between 50 mg to 100 mg. T_{max} values were consistent with the *in vitro* dissolution data showing that up to 80% of the drug was released from Oravig tablets within 6-8 hours. Adhesion time, tolerability, and acceptability for Oravig 50 mg were appeared to be more preferable compared with Oravig 100 mg. These results support the appropriateness of the proposed dose, dosing schedule, safety and tolerability of Oravig 50 mg as well as the 6 hours cut off point for reapplication.

The very low systemic absorption of miconazole through the buccal mucosa or the gastrointestinal tract after application of Oravig 50 mg was observed. Therefore, there is no or a low safety concern with systemic exposures, and the potential for drug-drug interactions will be minimal.

4.3. OCPB Filling/Review Form

Office of Clinical Pharmacology *New Drug Application Filing and Review Form*				
General Information About the Submission				
	Information			Information
NDA/BLA Number	22-404		Brand Name	Oravig®
OCP Division (I, II, III, IV, V)	IV		Generic Name	Miconazole
Medical Division	DSPTP		Drug Class	antifungal
OCP Reviewer	Yoriko Harigaya, Pharm.D.		Indication(s)	Treatment of oropharyngeal candidiasis
OCP Team Leader	Philip M. Colangelo, Pharm.D., Ph.D		Dosage Form	buccal tablet
Pharmacometrics Reviewer	N/A		Dosing Regimen	QD for 14 days
Date of Submission	June 15, 2009		Route of Administration	Buccal administration
Estimated Due Date of OCP Review	July 15, 2009		Sponsor	BioAlliance Pharma
Medical Division Due Date	N/A		Priority Classification	Standard
PDUFA Due Date	N/A			
Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				

single dose:	X	1		
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	2		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				

BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		

Yoriko Harigaya, Pharm.D.

Reviewing Clinical Pharmacologist DCP4/OCP/OTS Date

Philip Colangelo, Pharm.D., Ph.D.

Team Leader/Supervisor DCP4/OCP/OTS Date

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22404	ORIG-1	BIOALLIANCE PHARMA	Lauriad (miconazole [redacted] (b) (4) tablet)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YORIKO HARIGAYA
04/13/2010

PHILIP M COLANGELO
04/13/2010

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-204**	**Brand Name**	(b) (4)
OCP Division (I, II, III, IV, V)	**IV**	**Generic Name**	**Miconazole**
Medical Division	**DSPTP**	**Drug Class**	**antifungal**
OCP Reviewer	**Yoriko Harigaya, Pharm.D.**	**Indication(s)**	**Treatment of oropharyngeal candidiasis**
OCP Team Leader	**Philip M. Colangelo, Pharm.D., Ph.D**	**Dosage Form**	(b) (4) **buccal tablet**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**QD for 14 days**
Date of Submission	**June 15, 2009**	**Route of Administration**	**Buccal administration**
Estimated Due Date of OCP Review	**July 15, 2009**	**Sponsor**	**BioAlliance Pharma**
Medical Division Due Date	**N/A**	**Priority Classification**	**Standard**
PDUFA Due Date	**N/A**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		
multiple dose:				
Patients-				
single dose:				
multiple dose:	**X**	**1**		
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD -				
Phase 2:				
Phase 3:				
PK/PD -				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies				
Bio-waiver request based on BCS				
BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies				
Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**2**		

On **initial** review of the NDA/BLA application for filing:

	Content Parameter	Yes	No	N/A	Comment
Criteria for Refusal to File (RTF)					
1	Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			√	
2	Has the applicant provided metabolism and drug-drug interaction information?			√	
3	Has the sponsor submitted bioavailability data satisfying the CFR requirements?			√	
4	Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?	√			
5	Has a rationale for dose selection been submitted?	√			
6	Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?	√			
7	Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?	√			
8	Is the electronic submission searchable, does it have appropriate	√			

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?				
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
	Data				
9	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?			√	
10	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?			√	
	Studies and Analyses				
11	Is the appropriate pharmacokinetic information submitted?	√			
12	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?			√	
13	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?			√	
14	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?			√	
15	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			√	
16	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			√	
17	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	√			
	General				
18	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	√			
19	Was the translation (of study reports or other study information) from another language needed and provided in this submission?			√	

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?
Yes

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Reviewing Clinical Pharmacologist Date

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YORIKO HARIGAYA
08/18/2009

PHILIP M COLANGELO
08/18/2009

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA/BLA Number	**22-204**	**Brand Name**	**(b) (4)**
OCP Division (I, II, III, IV, V)	**IV**	**Generic Name**	**Miconazole**
Medical Division	**DSPTP**	**Drug Class**	**antifungal**
OCP Reviewer	**Dakshina M. Chilukuri**	**Indication(s)**	**Treatment of oropharyngeal candidiasis**
OCP Team Leader	**Philip M. Colangelo**	**Dosage Form**	**(b) (4) buccal tablet**
Pharmacometrics Reviewer	**N/A**	**Dosing Regimen**	**QD for 14-21 days**
Date of Submission	**February 6, 2009**	**Route of Administration**	**Buccal administration**
Estimated Due Date of OCP Review	**September 30, 2009**	**Sponsor**	**BioAlliance Pharma**
Medical Division Due Date	**N/A**	**Priority Classification**	**Standard**
PDUFA Due Date	**N/A**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.				
Tabular Listing of All Human Studies				
HPK Summary				
Labeling				
Reference Bioanalytical and Analytical Methods				
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:		**X**		
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

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BCS class				
Dissolution study to evaluate alcohol induced dose-dumping				
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Genotype/phenotype studies				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		**1**		

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CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

	hyperlinks and do the hyperlinks work?				
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Reviewing Clinical Pharmacologist Date

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

Team Leader/Supervisor Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dakshina Chilukuri
4/6/2009 12:08:56 PM
BIOPHARMACEUTICS

Phil, this is the filing checklist for Lauriad -
the applicant has been sent a RTF letter

Phil Colangelo
4/6/2009 02:27:08 PM
BIOPHARMACEUTICS